Testimony of Sidney M. Wolfe MD, Director, Public Citizen's Health Research Group, before Drug Safety and Risk Management/Reproductive Health Drugs Advisory Committees: December 9, 2011

There is no dispute that higher levels of ethinyl estradiol (EE) exposure can have serious adverse health consequences in women, including higher rates of venous thromboembolism (VTE). An FDA advisory committee, the predecessor to the Reproductive Health Drugs Advisory Committee, had concluded by 1988 that "efficacy for the prevention of pregnancy is the same for all oral contraceptives equal to or greater than 30 mcg of estrogen" and that high-dose oral contraceptives were not of "sufficiently unique value in clinical practice to warrant their continued availability for contraception."[1] A 1991 study of Michigan Medicaid cases by former FDA epidemiologist Dr. Burt Gerstman found the following[2]:

TABLE 1. Rates of deep venous thromboembolic disease in oral contraceptive estrogen dose-defined cohorts

Estrogen-defined cohorts (μg)	No. of cases	Person-years (× 10,000)	Rates/ 10,000 person-years
<50	53	12.7	4.2
50	69	9.8	7.0
>50	20	2.0	10.0
All	142	24.5	5.8

Currently, among the more than 60 pills on the market, all have a maximum of only 35 mcg of EE or less. Indeed, according to a standard pharmacological textbook, hormonal contraception should consist of the "minimum dosage of steroids that provides effective

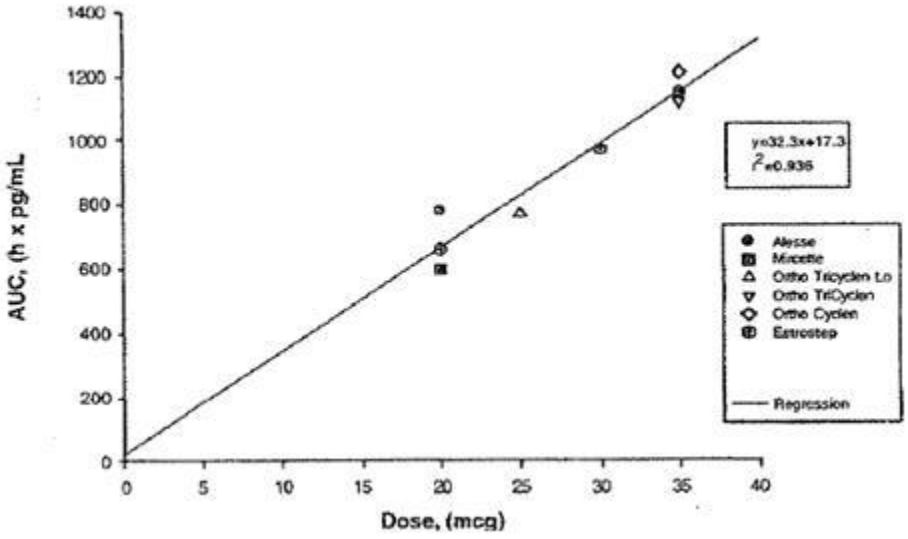
[1] Food and Drug Administration, Transcript of the Fertility and Maternal Health Drugs Advisory Committee. Volume II. January 15, 1988, P.166.

[2] Gerstman B. Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease. Am. J. Epid. 1991;133:32-7.

contraceptive coverage. This is often a pill with 30 to 35 mcg of estrogen, but preparations with 20 mcg may be adequate."[3]

Significantly Elevated AUC/EE Exposure Compared to Currently Available Pill Exposure

Figure 1B: EE Dose vs. AUC0-24 for Six Oral Contraceptive Pills[4]



There is clearly a relationship between the total amount absorbed as measured by the area under the curve (AUC) and the pill dose in mcg of EE as shown in the figure above. This relationship, according to Johnson and Johnson data from 1999, approaches linearity. Nevertheless, the issue of how much estrogen is delivered by the patch has been disputed by the company, initially arguing, in the first label, that the exposure was no more than you would get with a 20 microgram EE pill, despite AUC Patch values consistent with much higher EE doses.

From Table 6 of the FDA briefing package for today's meeting are the comparisons between the AUC for the Patch and the AUC for comparable oral contraceptives (OCs).

For the four comparator OCs (with EE concentrations ranging from 20 to 35 mcg), the ratios of the AUC of the EE in the patch to that of the OC were: 1.57, 2.1, 2.8 and 3.1,

[3] Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th Ed. 2001. McGraw Hill.
[4] Johnson & Johnson Pharmaceutical Research Institute. "Clinical Study Report Protocol NRGEEP-PHI-017; Phase 1." June 11, 1999. In re: Ortho Evra Products Liability Litigation, MDL 1742, N.D. Ohio, Case No. 1:06-cv-40000, Ex.591.

Table 6: Relative EE Exposure (AUC) Comparison between Ortho Evra and Select COCs

Study #	OC comparators[a]	EE AUC Ratio of patch/OC	EE C_{max} Ratio of patch/OC
NED-1	Cilest – 35 µg EE	1.57	0.73
PHI-017	Triphasil – 30 µg EE[b]	2.1	0.87
	Alesse – 20 µg EE	2.8	1.09
	Mercilon – 20 µg EE	3.1	1.07

[a]COC comparators contain EE and different progestins;
[b]Triphasil is a triphasic product containing 30 µg EE for 6 days, 40 µg EE for 5 days, and 30 µg EE for 10 days. PK sampling was done on days 15 – 21 for this comparison.

showing a consistently higher EE exposure for the patch.

The FDA's interpretation of these studies was:

"In Study NED-1, EE exposure (based on AUC values) in volunteers treated with Ortho Evra was 60% higher than that in volunteers treated with a [combination oral contraceptive (COC)] (Cilest) containing 35 µg EE. In Study PHI-017, EE exposure in volunteers treated with Ortho Evra was 2-3 fold higher than that in volunteers treated with daily Triphasil, Alesse, or Mercilon (COCs containing 20-30 µg of EE)."

Consistent with this would be the interpretation that the EE exposure delivered by the Patch is equivalent to twice that of the 30 mcg pill, or about three times that of the 20 mcg pill, in each case being roughly equivalent to an exposure delivered by 60 mcg of EE. A pill delivering such an exposure would never be approved. Was the FDA fully aware of these details about this mega-dose Patch before approval?

Increased Risk of VTE

The following chart, also from the FDA briefing package (page 38), summarizes the increased VTE risk in the various epidemiological studies:

Table 13 Relative Risk of VTE for Ortho Evra Users in the Various Studies

Study/Database	Comparator	Relative Risk	95% CI
I3 Ingenix[12]	NGM	2.0[a]	1.2-3.3
BCDSP, PharMetrics	NGM	1.2[b]	0.9-1.8
BCDSP, PharMetrics	LNG	2.0[c]	0.9-4.1
BCDSP, MarketScan	LNG	1.3[d]	0.8-2.1
FDA	LNG, NGM, NETA	1.6[e]	1.2-2.1
FDA	LNG[f]	1.3[e]	1.0-1.8

NGM = norgestimate; NETA = norethindrone acetate

[a] Approximated by odds ratio, for chart-verified cases, idiopathic and non-idiopathic, based on all pooled data from all phases of the study

[b] Approximated by odds ratio for nonfatal, idiopathic cases, based on pooled data from all phases of the study

[c] Approximated by odds ratio for idiopathic VTEs

[d] Approximated by odds ratio for idiopathic and non-idiopathic VTEs

[e] Approximated by hazard ratio for All Users adjusted for age, site, and year of study entry, based on all VTEs (inpatient and outpatient)

[f] LNG-containing COCs with 30 μg EE

The several earlier epidemiological studies showing increased VTE with the Ortho Evra Patch have been recently confirmed by the new FDA/Kaiser study, which had the following conclusions:

"The main findings of this study are that all use of the DRSP pill and **each of the continuous exposure preparations, the NGMN patch** and the ETON vaginal ring, are associated with an increased risk of VTE relative to the standard low-dose OCPs.

"The positive finding for the NGMN patch in relation to VTE provides an additional piece of evidence that this is a causal association, though there are few studies published that address this question (references 11-13 represent one study, while14, 16-17 represent one study)."[5]

The specific FDA/Kaiser findings for the Patch were: "For all users, the risk of VTEs was higher than 1 with each of the study CHCs relative to the grouped comparators for all use, ranging from 1.55 (95% CI 1.17 - 2.07) for the NGMN Patch," and "for NGMN, duration of >12 months of new use was associated with a 3-fold increase in risk [3.05 (1.23, 7.53)] of VTE relative to >12 months of combined comparator use."[6]

For all users, the risk of VTEs was higher than 1 with each of the study CHCs relative to the grouped comparators for all use, ranging from 1.55 (95% CI 1.172.07) for the NGMN patch.

[5] FDA/Kaiser Study, **Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints** page 29

[6] FDA/Kaiser Study, **Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints** page 27

From Table 12A of the FDA/Kaiser study, it can be seen that, relative to all COC users, the increased risk of hospitalized VTE was even greater than the risk of all VTE[7]:

	All VTE	Hospitalized VTE	
NGMN	1.31 (0.63, 2.74)	**1.55 (1.17, 2.07)**	**1.69 (1.19, 2.42)**

Serial Label Changes Reflect Belated Admissions of Greatly Increased EE Exposure and Increased VTE Risk

A history of the company's sometimes reluctantly agreed-upon label changes is instructive concerning the delayed admission of increased EE exposure and an increased risk of VTE.

The label for Ortho Evra has had 12 different changes since the original label, approved in November 2001. The following six label changes are the ones most relevant to the increased EE exposure and the concomitant increased risk of VTE.

- 2001 November 20: Original label: "The results indicated that **the average dose of norelgestromin and EE absorbed into the systemic circulation is 150 mcg/day and 20 mcg/day, respectively."**

- 2005 May 06: "This level of transdermal release of EE results **in exposure to EE greater than that produced by an oral contraceptive product containing 20 micrograms of EE."**

- 2005 November 10: "**Under steady-state conditions, AUC0-168 and [steady state concentration] for EE were approximately 55% and 60% higher, respectively, for the transdermal patch." Also added bold warning that:**

  "**AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing EE 35 µg**.

  (The statement in the original label, that "The results indicated that the average dose of norelgestromin and EE absorbed into the systemic

[7] FDA/Kaiser Study, **Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints** page 53

circulation is 150 mcg/day and 20 mcg/day, respectively," is now eliminated from this label.)

Previous labels had a general discussion about increased VTE with all hormonal contraceptives and included the statement that "It is unknown if the risk of venous thromboembolism with ORTHO EVRA® use is different than with use of combination oral contraceptives."

- 2006 September 20: **NEW LABEL (For the first time, this specific VTE risk information is added on Ortho Evra, in addition to the above VTE risk with *all* hormonal contraceptives):**

  "The risk of venous thromboembolism (VTE) in users of ORTHO EVRA® compared to users of oral contraceptives containing norgestimate and 35 mcg of EE was assessed in **two epidemiological studies** with a nested case control design conducted in the U.S. in women from ages 15 to 44 years. Both studies were conducted using electronic health care claims data. **One of these studies, which also included patient chart review, found an increased risk of VTEs for current users of ORTHO EVRA® compared to current users of the oral contraceptives. The odds ratio for current users in this study was 2.4 (95% CI 1.1 – 5.5). The other study did not find an increase in risk of VTEs for current users of ORTHO EVRA® (odds ratio 0.9 [95% CI 0.5 - 1.6]).**"

- 2008 January 18: NEW ADDITION TO PREVIOUS LABEL is Table 5, page 13 with results of all three studies, **including change from OR 0.9 to OR 1.1 in Jick study**.

- 2008 October 30: **Label change** adds another update from Jick, which makes the cumulative odds ratio 1.2 (Table 5, page 13).

- **2011** March 23: Label adds a black box warning of an increased risk of VTE based on the epidemiology studies and moves the black box to the beginning of the label. In fact, the entire first page is now a black box.

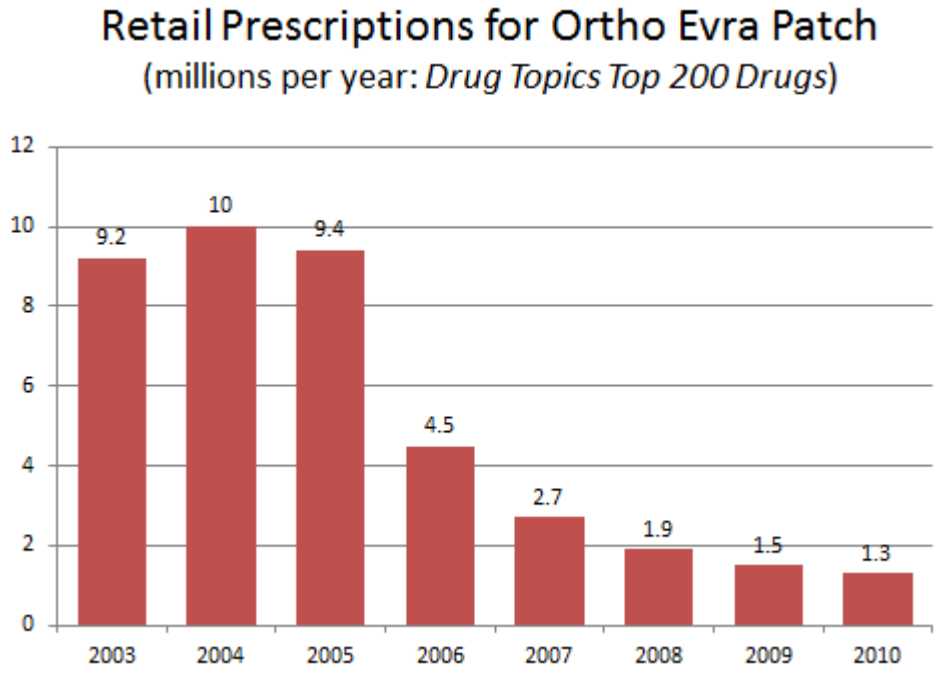
  From the black box warning: VTE RISK: **The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA® patch compared to women who used oral contraceptives containing 30-35 mcg of ethinyl estradiol (EE) and either levonorgestrel or norgestimate was assessed in four U.S. case-control studies using electronic healthcare claims data. The odds ratios ranged from 1.2 to 2.2; one of the studies**

found a statistically significant increased risk of VTE for current users of ORTHO EVRA® (see WARNINGS -Table 5).

Response of Prescribers to New EE Dose and VTE Risk Information

The chart below tracks the annual retail prescriptions filled for the Ortho Evra Patch and shows the correlation of significant decreases in prescribing with "new" information appearing on the label and other warnings by the FDA. The decline began in 2005 with the statements that year that "**AUC and average concentration at steady state for ethinyl estradiol (EE) are approximately 60% higher in women using ORTHO EVRA® compared with women using an oral contraceptive containing EE 35 µg**."

By 2006, the number of prescriptions filled had fallen another 50 percent from the previous year, also accompanying the first admission in the label of a study showing increased VTE risk. By 2010, with additional warnings, the number of prescriptions was only 13 percent of the maximum of 10 million in 2004.



Strength of the Relationship Between the High Estrogen Dose Ortho Evra Patch and VTE — Some Bradford Hill Principles

Temporal Relationship: The cause clearly precedes the effect.

Statistical Significance/Strength of Relationship: Several studies have found the relationship statistically significant.

Repeat Observations/Consistency: Several studies have now documented this increased risk.

Biologic Plausibility: The effect of estrogens on blood clotting is well-documented.

Dose Response Effect: The study of Gerstman et al has documented the relationship between higher dose and greater risk of DVT.

Options for These Committees and for the FDA

The sharp decrease in prescriptions for the Ortho Evra Patch with additional warnings about EE exposure and evidence of increased VTE risks could be viewed as the market place working, e.g., who needs FDA to ban such a drug? The other way of looking at this is to reflect on a discussion held last week during a meeting of our Drug Safety and Risk Management Committee concerning approaches to Risk Evaluation and Management Strategies (REMS). A presentation concerning various levels of risk prevention began with the most effective strategy, banning the substance, and continued to less effective strategies, including labeling.

If a product, in this case a drug, has no unique benefits and, relative to equally effective lower-dose EE containing OCs, more risk of VTE, there is no reason to leave it on the market. The 87 percent decrease in Patch prescribing between 2004 and 2010 means many more women are being protected from this riskier product but the women still getting the product — 1.3 million prescriptions in 2010 — are still at increased risk with no significant, documented offsetting benefit.

The main — related — questions to be asked are

A. Is there any evidence of a unique benefit? And, especially if not;

B. Do we adhere to the precautionary principle regarding the documented risks of the Ortho Evra Patch and advocate a phased withdrawal of the product?